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Health and Environmental Effects Profile for Ethylene Thiourea

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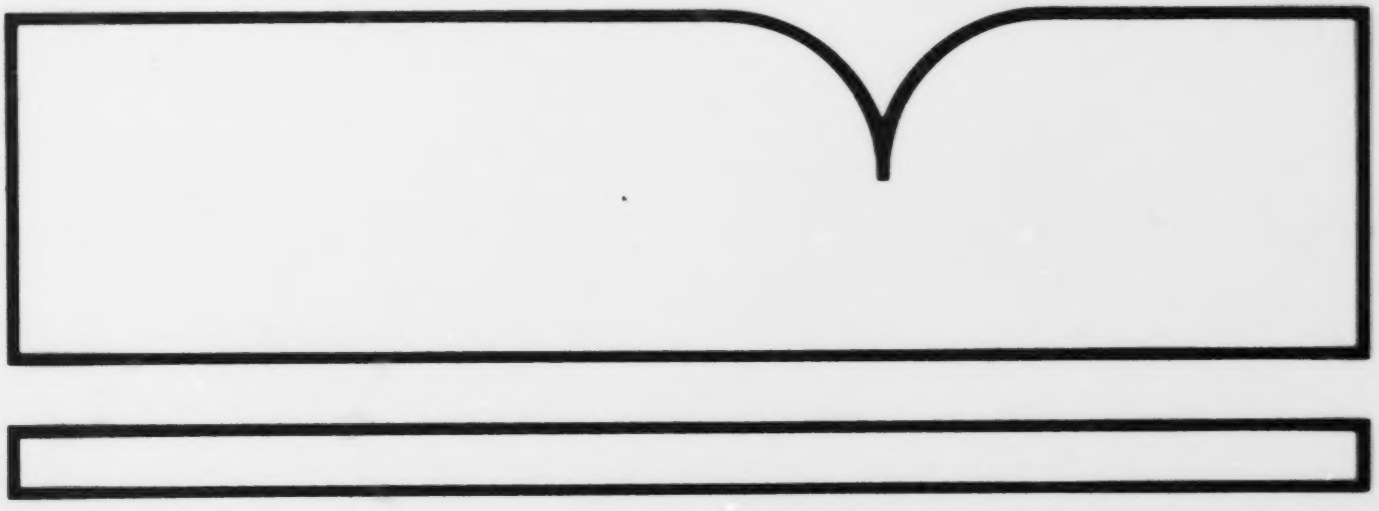

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ETHYLENE THIOUREA

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for ethylene thiourea was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Ethylene thiourea has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for ethylene thiourea is 1.8×10^{-1} (mg/kg bw/day)$^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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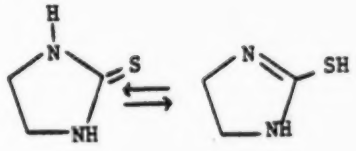
LIST OF ABBREVIATIONS

CNS	Central nervous system
cpm	Counts per minute
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MTD	Maximum tolerated dose
NADPH	Reduced Nicotinamide Adenine Dinucleotide Phosphate
ppm	Parts per million
TLC	Thin layer chromatography
TSH	Thyroid-stimulating hormone
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Ethylene thiourea (ETU) is the common name for 2-imidazolidinethione. This compound is also known as 4,5-dihydroimidazole-2(3H)-thione; N,N'-ethylene-thiourea, 1,3-ethylene-2-thiourea, 2-imidazoline-2-thiol, 2-mercaptoimidazole and 2-thiol-dihydroglyoxine. It is produced under the following trade names: NA-22, NA-22-D, Pennac CRA, Sodium-22 neoprene accelerator and Warecure C (NIOSH, 1983; IARC, 1974). The structure of ETU is given below (IARC, 1974):



Molecular formula: $C_3H_6N_2S$

Molecular weight: 102.2

The Chemical Abstracts Service (CAS) Registry Number for this compound is 96-45-7.

1.2. CHEMICAL AND PHYSICAL PROPERTIES

ETU is a white, crystalline solid with the following physical properties:

Melting point:	203-204°C (Windholz, 1976)
Solubility:	in 100 mℓ of water -- 2 g at 30°C, 9 g at 60°C and 44 g at 90°C; moderately soluble in methanol, ethanol, ethylene glycol and pyridine; insoluble in acetone, ether, chloroform, benzene and ligroin (Windholz, 1976).
Log octanol/water partition coefficient:	-0.66 (Hansch and Leo, 1981)

1.3. PRODUCTION DATA

ETU is produced by Fike Chemical, Inc., Nitro, WV, with an annual production volume of between 100,000 and 1,000,000 pounds/year (U.S. EPA, 1977; SRI, 1983). The 1982 Directory of Chemical Producers (SRI, 1982) also lists Pennwalt Corp., Wyandotte, MI, as a producer of ETU. The 1977 TSCA Production file (U.S. EPA, 1977) also lists the following importers:

Importer	Location	Volume (lbs/year)
Akron Chemical Co.	Akron, OH	10,000-100,000
Henley and Co, Inc.	New York, NY	no report
Mobay Chemical Corp.	Pittsburgh, PA	no report
Millmaster Chemical Co.	Berkeley Heights, NJ	<1000
Prochimie International, Inc.	New York, NY	10,000-100,000

The synthesis of ETU may be accomplished by reacting ethylenediamine with carbon disulfide, followed by ring closure by refluxing with hydrochloric acid (Johnson and Edens, 1942); however, it is unknown if it is produced commercially by this route (IARC, 1974).

1.4. USE DATA

The primary use of ETU is as a curing agent for epichlorohydrin elastomers (Vanderberg, 1979) and as an accelerator for neoprene rubber (IARC, 1974).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Although ETU is used primarily in the rubber and plastics industry, it is introduced into the environment because it is a degradation product of ethylenebisdithiocarbamate fungicides, such as maneb and zineb (IARC, 1974), and it is also an impurity of at least 28 formulations of these agricultural chemicals (Bontoyan et al., 1972).

The fate and transport of ETU in soil have been studied by several investigators. Removal of ETU from soil by microbial degradation with the release of CO_2 was reported by Lyman and Lacoste (1975), but only an abstract of the study was available, so further details were lacking. Kaufman and Fletcher (1973) found that 2 days after application of 20 ppm ^{14}C-ETU to Hagerstown silty clay loam or Lakeland sandy loam, all the radiolabel was present as ethyleneurea, 43% of which was degraded to $^{14}CO_2$ by the fourth day. Results using autoclaved soil indicated that the conversion of ^{14}C-ETU to ^{14}C-ethyleneurea was accomplished chemically (perhaps by reaction with free radicals since degradation of ETU by Fenton's reagent was rapid), while further degradation to CO_2 was accomplished microbially.

In a field study in Delaware, Rhodes (1977) found that when ^{14}C-ETU was applied at a rate of 2 pounds/acre to 4-inch diameter sections of soil (Keyport silty loam) isolated by 12-inch long sections of stainless steel tubing driven into the ground (runoff was prevented by a protruding lip), the total ^{14}C residues disappeared with a half-life of <4 weeks. The half-life for disappearance of intact ETU was actually <1 week. The total rainfall for the 1-week period was 0.56 inches. Most of the radioactivity was confined to the top 1-5 inches of the soil column; however, detectable

amounts (0.2%) were found in depths of 8-12 inches by 12 weeks after application. After 52 weeks 16% of the initial radio activity was present in the top 1 inch, 4% in 1-3 inches, 1.0% in 3-5 inches, 0.5% in 5-8 inches and 0.1% in 8-12 inches (total rainfall for 52 weeks was 54 inches). ETU did not, therefore, leach to any great extent under these conditions. The overall half-life for the degradation products (hydantoin, ethyleneurea, Joffe's base and glycine) was 4 weeks. Some of the degradation may have occurred by microbial action, but this was not investigated. Blazquez (1973) sprayed ETU on the surface of prepared soil beds (Immokalee fine sand) at a rate of 2 pounds/100 gallons of water and found that ~47% disappeared after 1 day, 60% by 6 days, 69% by 13 days, and only a trace was detected after 27 days. No statement was made regarding the mechanism of disappearance.

In soil mobility studies using ^{14}C-ETU, Helling and Thompson (1974) reported the R_f values for the compound when leached onto soil TLC plates to be 0.96 in Norfolk sandy loam, 1.00 in Lakeland sandy loam, 0.96 in Hagerstown silty clay loam, 0.83 in Barnes clay loam and 0.61 in Celeryville muck. The organic matter content of the first five soil types ranged from 0.14-6.9%, while Celeryville muck contained 90.4%. Thus, ETU was very leachable except on soil with high organic matter content. ETU was immobilized by drying the soil or by incubating the compound prior to leaching, indicating that ETU was either irreversibly adsorbed or substantially degraded. These authors also found no indication of photodegradation of ETU when the soil plates were exposed to continuous fluorescent illumination.

Upon incubation or drying, the immobile origin spot, identified as ethyleneurea, increased (Helling and Thompson, 1974). Experiments using moist stored soil (microbially active) or dry stored soil (microbially inactive) shaken with nutrient broth failed to confirm microbial degradation.

Only 10% of 1.5 ppm ^{14}C-ETU aqueous solution, shaken with 1 g of Hagerstown soil, was adsorbed within 2 hours. By 66 hours, 25% was adsorbed. This weak adsorbtion property in moist soils is consistent with the high leaching ability of ETU (Helling and Thompson, 1974).

In microagroecosystem chamber studies, Nash and Beall (1980) reported "half-life" values (time to reduce the maximum chemical concentration at application by one-half for ETU in Galestown sandy loam (pH 6.7; organic matter content, 5.3%) of 3 days when generated from maneb, and 0.5 days when generated from zineb when these fungicides were sprayed on tomato plants growing in the chambers. ETU was detectable only on the first 2 days following fungicide treatment. Thus, ETU is weakly adsorbed to soil, is highly mobile in moist soil, but is immobilized by dry soil. Degradation appears to be accomplished readily by both chemical and biological means and, thus, ETU does not persist in soil.

Since ETU has a relatively high water solubility, it is likely to enter the aquatic environment through runoff and leaching through soil. Removal from water may be accomplished by chemical reactions, photolysis or microbial degradation.

The hydrolysis of ETU has been studied by several investigators. Blazquez (1973) reported residual concentrations of 100 ppm ETU in 1000 mℓ of deionized water maintained at 20°C to be 95% by day 1, 80% by day 7 and 50% by day 21. In ditches containing 500 g ETU/946 ℓ of water, 50% disappeared in 1 day, 75% in 7 days and ~90% in 14 days. Cruickshank and Jarrow (1973), however, reported that ETU was not readily degraded in 1% aqueous solutions at pH 5, pH 7 or pH 9 when held at room temperature or at 90°C for as long as 3 months. These investigators demonstrated that photolysis of ETU is a major pathway of degradation. ETU was slowly degraded when exposed to near UV light (>285 nm) on silica gel (100 $\mu g/cm^2$).

This degradation was greatly enhanced by the addition of 1-acetonaphthone as a sensitizer, with 70% loss of ETU occurring after 20 hours of exposure. When irradiated with a GE sunlamp for 20 hours, degradation of 1 µg ETU/cm² was 99% in the presence of the sensitizer. Identified as photolysis products were bis (imidazalin-2-yl) sulfide and 2-imidazolidone (ethyleneurea).

Ross and Crosby (1973) found that exposure of solutions of ETU (0.5-50 mg/ℓ) in deionized water to summer sunlight or to UV light (F40 BL GE lamp) resulted in no photolysis except in the presence of acetone (5 mg/ℓ) or other sensitizers (95% loss from 0.64 mg/ℓ solutions after 4 hours of exposure). Boiled agricultural drainage ditch water samples fortified with ETU at 0.5 mg/ℓ resulted in 50-90% degradation following irradiation by lamp for 3 days or by sunlight for 24 hours indicating that natural photosensitization may play an important role in photodegrading ETU in natural water. No degradation was observed after exposure to darkness. The products of photodegradation were identified as ethyleneurea and glycine sulfate.

Rhodes (1977) reported that exposure of aqueous solutions of ^{14}C-ETU to a mercury vapor UV lamp resulted in 99% degradation after 6 hours, and after 3 hours in the presence of 0.1 M acetone as sensitizer. The products were identified as glycine sulfate, ethyleneurea, hydantoin and Jaffe's base.

No information regarding microbial degradation of ETU in aquatic media was found, but extrapolation from the soil data may be appropriate. Also, information concerning the bioconcentration of ETU was not encountered, but a low tendency for bioconcentration can be predicted from the low value of the log octanol-water partition coefficient, -0.66 (Hansch and Leo, 1981).

The only information regarding the fate or transport of ETU in the atmosphere was reported in a study of the fate of maneb and zineb in microagroecosystem chambers (Nash and Beall, 1980). Air from chambers in which tomato plants sprayed with the fungicides were growing was trapped by polyurethane foam filters and analyzed for the parent compounds as well as for the degradation product, ETU. The results indicated that ETU was volatile, comprising ~10% of the volatilized components, and had a "half-life" of 8-9 days in air. The concentration in the chamber air was ~1 ng/m^3 on the first day after application and declined rapidly after 7 days, perhaps due to sprinkle irrigation reduction of ETU levels.

Although from the results of Nash and Beall (1980) ETU appears to be volatile, its high solubility, ability to undergo photolysis in the presence of natural sensitizers, and its expected degradability by chemical means (free radical reactions and hydrolysis) indicate that any ETU entering the atmosphere through volatilization would be partly removed from the air by rain, and would be partly degraded by photochemical or chemical means.

3. EXPOSURE

No monitoring data on ETU were contained in STORET, and no other information regarding ambient levels in air, water or soil was available.

Human exposure to ETU is primarily the result of residual ethylenebis dithiocarbamate fungicides on food crops. Of 167 food samples produced in or imported by Canada, 56 contained detectable levels of ETU ranging from $\leq$0.02 ppm for most items to 0.047 and 0.083 ppm for canned spinach and orange peel, respectively (Pecka et al., 1975). Although little, if any, residual ETU was found on harvested apples, tomatoes, grapes, pears, potatoes, cucumbers, squash or cantaloupes, the cooking, processing and storing of such foods have resulted in detectably increased levels (Ross et al., 1978; Ripley and Cox, 1978; Ripley et al., 1978; Ripley and Simpson, 1977; Pease and Holt, 1977; Uno et al., 1978; Cseh-Szepessy, 1978; Watts et al., 1974).

It has been shown that the ethylenebisdithiocarbamate fungicides degrade to ETU at high temperature and humidity (Bontoyan and Looker, 1973) and when stored (Petrosini et al., 1963; Stanculescu et al., 1979).

4. PHARMACOKINETICS

4.1. ABSORPTION

Rats receiving a single oral dose of 40 mg ^{14}C-ETU/kg excreted 82% of the administered radioactivity in the urine; 90% of the urinary radioactivity was excreted in the first 24 hours. The majority of radiocarbon given orally to two rhesus monkeys at a dose of 40 mg ^{14}C-ETU/kg was excreted in the urine (47 and 64%) in 48 hours (Allen et al., 1978). These elimination data indicated that most of the ETU dose was absorbed by the GI tracts of the rats and monkeys.

Absorption of ETU from the GI tracts of pregnant mice and rats was rapid. Peak plasma levels of radioactivity were achieved at 1.4 and 1.3 hours, respectively, post-treatment with 240 mg ^{14}C-ETU/kg administered orally to mice or rats and 240 mg ^{35}S-ETU/kg to rats (Ruddick et al., 1976a,b, 1977). Kato et al. (1976) reported similar results in pregnant rats treated orally with 100 mg ^{14}C-ETU/kg. Radioactivity was detected in the blood as early as 5 minutes, increasing rapidly to peak levels at 2 hours.

Teshima et al. (1981) reported relatively slow absorption of ETU from application to intact skin of guinea pigs. No information on dose levels was provided in the available abstract.

4.2. DISTRIBUTION

The distribution of radioactivity from ^{14}C-ETU has been studied in rats, mice, guinea pigs, monkeys, and pregnant rats and mice.

Allen et al. (1978) found very little accumulation of radiocarbon in muscle, blood, skin and liver of rats (0.73%) 48 hours after oral dosing with 40 mg ^{14}C-ETU/kg (the position of the label was not specified);

however, rhesus monkeys retained ~25% of the administered dose, with the greatest accumulation in muscle (11.6%). Newsome (1974) reported a range of residue levels of ETU, detected by gas-liquid chromatography in liver, kidney, heart and muscle, of 0.010-0.086 ppm in rats and guinea pigs 96 hours following oral doses of 20 mg ETU/kg; the thyroid levels were considerably higher at 0.824 ppm in rats and 0.75 ppm in guinea pigs. Thyroid accumulation of ETU in guinea pigs was also reported in an abstract of a study by Teshima et al. (1981).

Ruddick et al. (1976b) noted in pregnant rats treated with ^{14}C-ETU at doses of 240 mg/kg on day 11, 12 or 15 of gestation that radiolabel binding to red blood cells was reversible and that label did not accumulate in blood, livers or kidneys of the dams or the fetuses. The radioactivity detected in fetuses appeared to be uniformly dispersed. Similar results were obtained by Kato et al. (1976) on the distribution of [2-^{14}C]-ETU in pregnant rats and fetuses; however, examination of the thyroid revealed accumulation of radiocarbon in this tissue, with levels of radioactivity equivalent to 0.346, 0.483 and 0.651 µmole ETU/g tissue at 2, 6 and 24 hours, respectively, after dosing with 100 mg [2-^{14}C]-ETU/kg (935 µmole/kg). Distribution of radioactivity in pregnant mice given a single oral dose of 240 mg [4,5-^{14}C]-ETU/kg was similar to that of rats at 3 hours after dosing, but the radioactivity was eliminated faster from mice than from rats (Ruddick et al., 1976a, 1977).

4.3. METABOLISM

The metabolism of ETU has been studied in mice, rats and cats in both <u>in vivo</u> and <u>in vitro</u> systems. Savolainen and Pyysalo (1979) identified the main urinary metabolite found in mice treated orally with [2-^{14}C]-ETU, [4,5-^{14}C]-ETU or ^{35}S-ETU at 67 mg/kg as 2-imidazolin-2-yl-sulfonate,

which contained all radiolabels. The same metabolite was found after in vitro incubation with mouse liver microsomal NADPH preparations. Metabolism was believed to occur via sulfoxidation of ETU. Ethyleneurea was also identified as a metabolite of ETU in mice.

In pregnant rats given [4,5-^{14}C]-ETU by gavage, $^{14}CO_2$ was expired, but only trace amounts of radiolabel were expired from rats given [2-^{14}C]-ETU. This indicated that CO_2 was formed from fragmentation of the imidazoline ring and the decarboxylation of the 4 or 5 carbon atom of ETU (Kato et al., 1976).

Rats treated with 4.0 mg/kg [4,5-^{14}C]-ETU excreted 82.7% of the radioactivity in the 24-hour urine, 62.6% of which was identified by TLC as unchanged ETU, 18.3% was ethyleneurea, 4.9% imidazolone, 1.9% imidazoline and 12.3% other metabolites (Iverson et al., 1980). In vitro formation of ETU and imidazolone using the rat liver microsomal-NADPH system suggested an oxidative desulfuration reaction (Iverson et al., 1980). High performance liquid chromatography of urine from ETU treated rats identified a thioimidazole, indicative of a dehydrogenation reaction without the formation of ethyleneurea. Other sulfur-containing metabolites identified by high performance liquid chromatography were thiohydantoin, N-methyl ETU and N-methyl thioimidazole (Iverson et al., 1979). Kobayashi et al. (1982) identified 1-methylthiourea in the plasma of rats 2 hours after a 200 mg ETU/kg oral dose. The TLC analysis of the 24-hour urinary metabolites from cats treated orally with 4 mg [4,5-^{14}C]-ETU/kg revealed 28.0% unchanged ETU, 3.5% ethyleneurea and 64.3% S-methyl ETU (not identified in rats), while no imidazolone or imidazoline were detected (Iverson et al., 1980).

4.4. EXCRETION

Rapid elimination of ETU in the urine of rats and guinea pigs was noted by Newsome (1974), with 18% of the administered dose eliminated at 6 hours and 43% at 24 hours from rats, and 18% at 6 hours and 27% at 24 hours from guinea pigs. Excretion was essentially complete at 48 hours. The feces of rats and guinea pigs contained negligible amounts of ETU. Allen et al. (1978) found that rhesus monkeys excreted ~50% of the administered dose of ^{14}C-ETU in the 48-hour urine, while at that time for rats, 82% of the radiolabel was detected. Similar findings for urinary elimination were found by Kato et al. (1976), who also found expiration of $^{14}CO_2$ from pregnant rats administered [4,5-^{14}C]-ETU. Elimination from plasma was biphasic with rapid loss by 4 hours, followed by a slower phase which was complete at 24 hours after dosing of rats with [2-^{14}C]-ETU (Kato et al., 1976). Ruddick et al. (1976b) calculated the half-life for plasma elimination (assuming first-order kinetics) for pregnant rats as 10 hours. Excretion of radioactivity at 12 hours after administration of 240 mg [4,5-^{14}C]-ETU/kg was ~50% complete from rats and ~60% complete from mice. By 48 hours, the total amount excreted (70-80%) was similar for the two species (Ruddick et al., 1976a, 1977).

Thus, it appears that ETU is rapidly absorbed upon oral dosing in several species, is metabolized with little accumulation in tissues except for the thyroid, and is eliminated rapidly. Elimination includes a substantial amount of unmetabolized ETU. There also appear to be some interspecies differences in metabolism.

5. EFFECTS

5.1. CARCINOGENICITY

An NTP (1983) bioassay for the carcinogenicity of ETU has begun, and the chronic test is in progress. The results of five chronic feeding studies in rats (Weisburger et al., 1981; Ulland et al., 1972; Graham et al., 1973, 1975) and one in two hybrid strains of mice (BRL, 1968; Innes et al., 1969) are summarized in Tables 5-1 through 5-5.

BRL (1968) and Innes et al. (1969) reported significantly increased incidences of hepatomas in both sexes of two strains of mice and significantly increased incidences of lymphoma in females of one strain when compared with controls. In comparison with pooled controls, dietary administration of ETU at the MTD (350 ppm) significantly ($p<0.05$) increased the incidence of thyroid follicular carcinoma in both male and female Charles River CD rats (Weisburger et al., 1981).

Ulland et al. (1972) also reported increased ($p<0.05$) thyroid carcinoma incidence in rats fed ETU at the MTD for 18 months.

Charles River rats developed thyroid gland carcinomas and adenocarcimas at dietary levels of 250 and 500 ppm when treated for 1 or 2 years (Graham et al., 1973, 1975). Further details of dose levels, exposure periods and tumor incidence are given in Tables 5-1 through 5-5.

An abstract of a French study (Gak et al., 1976) reported that ETU was not carcinogenic to hamsters fed up to 200 mg ETU/mg for life, but thyroid adenocarcinomas were induced by lifetime feeding of 60 mg ETU/kg to male mice and 200 mg ETU/kg to female mice.

In addition to the chronic feeding studies, BRL (1968) reported no significant increased tumor incidence in $B6C3F_1$ or $B6AKF_1$ male or female mice given a single subcutaneous injection of 1000 mg ETU/kg and killed and necropsied ~18 months later.

TABLE 5-1

Summary of Oral Carcinogenicity Study of BRL, 1968 and Innes et al., 1969

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
Mice/ B6AFK1	M	initially 215 mg/kg followed by 646 ppm	initially for 3 weeks by gavage followed by diet for 18 months	82 weeks	NR	initially 0.5% gelatin followed by incorporation into diet	lymphatic tissues	lymphoma	3/18
Mice/ B6AFK1	F	initially 215 mg/kg followed by 646 ppm	initially for 3 weeks by gavage followed by diet for 18 months	82 weeks	NR	initially 0.5% gelatin followed by incorporation into diet	lymphatic tissues	lymphoma	4/16*
Mice/ B6AFK1	M	0	NA	82 weeks	NA	NA	lymphatic tissues	lymphoma	1/90
Mice/ B6AFK1	F	0	NA	82 weeks	NA	NA	lymphatic tissues	lymphoma	4/82
Mice/ B6C3F1	M	initially 215 mg/kg followed by 646 ppm	initially for 3 weeks by gavage followed by diet for 18 months	83 weeks	NR	initially 0.5% gelatin followed by incorporation into diet	liver	hepatoma	14/16
Mice/ B6C3F1	F	initially 215 mg/kg followed by 646 ppm	initially for 3 weeks by gavage followed by diet for 18 months	82 weeks	NR	initially 0.5% gelatin followed by incorporation into diet	liver	hepatoma	18/18
Mice/ B6C3F1	M	0	NA	82 weeks	NA	NA	liver	hepatoma	8/79
Mice/ B6C3F1	F	0	NA	82 weeks	NA	NA	liver	hepatoma	0/87
Mice/ B6AFK1	M	initially 215 mg/kg followed by 646 ppm	initially for 3 weeks by gavage followed by diet for 18 months	82 weeks	NR	initially 0.5% gelatin followed by incorporation into diet	liver	hepatoma	18/18

TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
Mice/ B6AFK1	F	initially 215 mg/kg followed by 646 ppm	initially for 3 weeks by gavage followed by diet for 18 months	82 weeks	NR	initially 0.5% gelatin followed by incorporation into diet	liver	hepatoma	9/16
Mice/ B6AFK1	M	0	NA	82 weeks	NA	NA	liver	hepatoma	5/90
Mice/ B6AFK1	F	0	NA	82 weeks	NA	NA	liver	hepatoma	1/82

QUALITY OF EVIDENCE

Strengths of Study: The animals were initially exposed to the test compound at 7 days of age by gavage followed by dietary exposure to the compound for an appreciable portion of their lifespan.

Weakness of Study: The animal group size was small and only one dose level was used. Lymphomas were significantly (p=0.05) increased only in female mice of strain (C57BL/6 x AKR)F_1. Although hepatomas were increased significantly (p=0.01) in all strains and sexes, the authors stated that tumors designated as hepatomas should be considered to be mainly malignant.

Overall Adequacy: Adequate

*Information on missing mice is not available.

NA = Not applicable; NR = Not reported

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TABLE 5-2

Summary of Oral Carcinogenicity Study of Weisburger et al., 1981

Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
Rat/ Charles River CD	M	350 ppm	78 weeks	104 weeks	90%	diet	thyroid gland	follicular carcinoma papillary carcinoma	15/26 2/26
Rat/ Charles River CD	F	350 ppm	78 weeks	104 weeks	90%	diet	thyroid gland	follicular carcinoma papillary carcinoma	6/26 2/26
Rat/ Charles River CD	M	175 ppm	78 weeks	104 weeks	90%	diet	thyroid gland	follicular carcinoma papillary carcinoma	2/26 1/26
Rat/ Charles River CD	F	175 ppm	78 weeks	104 weeks	90%	diet	thyroid gland	follicular carcinoma papillary carcinoma	2/26 1/26
Rat/ Charles River CD	M	0 ppm	NA	104 weeks	NA	NA	thyroid gland	follicular carcinoma papillary carcinoma	0/20 0/20
Rat/ Charles River CD	F	0 ppm	NA	104 weeks	NA	NA	thyroid gland	follicular carcinoma papillary carcinoma	0/20 0/20

QUALITY OF EVIDENCE

Strengths of Study: The compound was tested by a natural route at two dose levels (MTD and one-half MTD). The animals were treated for a significant portion of their lifespan.

Weakness of Study: The matched control group was small (10 animals). However, no thyroid carcinomas were found in pooled controls, and only 1 follicular cell and 1 C-cell carcinoma were found in 184 male negative controls, and none was found among 184 female negative controls.

Overall Adequacy: Adequate

Comments: The incidence of thyroid follicular carcinoma was increased significantly ($p<0.02$) in both sexes at 350 ppm, but not at 175 ppm, in comparison to pooled controls.

NA = Not applicable

TABLE 5-3

Summary of Oral Carcinogenicity Study of Ulland et al., 1972

Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Primary Target Organ	Primary Tumor Type	Tumor Incidence (P value)
Rat/ Charles River CD	M	350 ppm	18 months	24 months	technical grade (97%)	diet	thyroid gland	thyroid carcinoma	17/26
							lung	metastases	2/26
Rat/ Charles River CD	F	350 ppm	18 months	24 months	technical grade (97%)	diet	thyroid gland	thyroid carcinoma	8/26
Rat/ Charles River CD	M	175 ppm	18 months	24 months	technical grade (97%)	diet	thyroid gland	thyroid carcinoma	3/26
Rat/ Charles River CD	F	175 ppm	18 months	24 months	technical grade (97%)	diet	thyroid gland	thyroid carcinoma	3/26
Rat/ Charles River CD	M	0 ppm	NA	24 months	NA	NA	thyroid gland	thyroid carcinoma	0/32
Rat/ Charles River CD	F	0 ppm	NA	24 months	NA	NA	thyroid gland	thyroid carcinoma	0/32

QUALITY OF EVIDENCE

Strengths of Study: The compound was tested by a natural route at two dose levels. The animals were treated for a significant portion of their lifespan.

Overall Adequacy: Adequate

NA = Not applicable

TABLE 5-4

Summary of Oral Carcinogenicity Study of Graham et al., 1975

Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Primary Target Organ	Primary Tumor Type	Tumor Incidence (P value)
Rat/ Charles River CD	NR	500 ppm	24 months	24 months	NR	diet	thyroid gland	carcinoma/adeno-carcinoma	62/70
							all tissues	malignant tumors	63/70
Rat/ Charles River CD	NR	250 ppm	24 months	24 months	NR	diet	thyroid gland	carcinoma/adeno-carcinoma	16/69
							all tissues	malignant tumors	31/69
Rat/ Charles River CD	NR	125 ppm	24 months	24 months	NR	diet	thyroid gland	carcinoma/adeno-carcinoma	2/73
							all tissues	malignant tumors	16/73
Rat/ Charles River CD	NR	25 ppm	24 months	24 months	NR	diet	thyroid gland	carcinoma/adeno-carcinoma	1/73
							all tissues	malignant tumors	13/73
Rat/ Charles River CD	NR	5 ppm	24 months	24 months	NR	diet	thyroid gland	carcinoma/adeno-carcinoma	2/75
							all tissues	malignant tumors	23/75
Rat/ Charles River CD	NR	0 ppm	NA	24 months	NA	diet	thyroid gland	carcinoma/adeno-carcinoma	2/72
							all tissues	malignant tumors	15/72

QUALITY OF EVIDENCE

Strengths of Study: The compound was tested by a natural route at five dose levels. The animals were treated for a significant portion of their lifespan.

Weakness of Study: The tumor incidence in each sex was not specified. The purity of the test compound was not stated. Tumor incidence was given only for rats tested for 24 months, and not for rats fed only 12 months. (See Table 5-5 for 12-month data of Graham et al., 1973.)

Overall Adequacy: Adequate

Comments: The authors state that ETU is a thyroid carcinogen for Charles River rats when fed at levels of 250 and 500 ppm in the diet for 2 years.

NA = Not applicable; NR = Not reported

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TABLE 5-5

Summary of Oral Carcinogenicity Study of Graham et al., 1973

Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Primary Target Organ	Primary Tumor Type	Tumor Incidence (P value)
Rat/ Charles River CD	M	500 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	10/13
Rat/ Charles River CD	F	500 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	5/12
Rat/ Charles River CD	M	250 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	3/13
Rat/ Charles River CD	F	250 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	0/10
Rat/ Charles River CD	M	125 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	0/11
Rat/ Charles River CD	F	125 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	0/11
Rat/ Charles River CD	M	25 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	0/11
Rat/ Charles River CD	F	25 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	0/10
Rat/ Charles River CD	M	5 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	0/11
Rat/ Charles River CD	F	5 ppm	12 months	12 months	NR	diet	thyroid	adenocarcinoma	0/10

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TABLE 5-5 (cont.)

Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Primary Target Organ	Primary Tumor Type	Tumor Incidence (P value)
Rat/ Charles River CD	M	0 ppm	NA	12 months	NA	NA	thyroid	adenocarcinoma	0/13
Rat/ Charles River CD	F	0 ppm	NA	12 months	NA	NA	thyroid	adenocarcinoma	0/9

QUALITY OF EVIDENCE

Strengths of Study: The compound was tested by a natural route at five dose levels to both males and females.

Weakness of Study: The study was conducted for only 1 year, but the data were reported for an interim kill during a 2-year study (See Table 5-4, Graham et al., 1975).

Overall Adequacy: Inadequate in light of the longer feeding study (see comment above).

Comments: The authors state that thyroid carcinomas were produced at doses of 250 and 500 ppm; under the conditions of this study ETU is a carcinogen.

NA = Not applicable; NR = Not reported

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An abstract of a human study on occupational exposure of female workers to rubber containing ETU reported no increased incidence of thyroid cancers (Smith, 1976)

5.2. MUTAGENICITY

Table 5-6 summarizes the results of many genotoxicity studies. ETU was positive in some strains of Salmonella typhimurium in the reverse mutation assay to histidine independence (Seiler, 1974; Schupbach and Hummler, 1977; Teramoto et al., 1977), in B. subtilis spores in the rec assay (Kada, 1981), in a cell transformation assay with hamster kidney cells (Daniel and Dehnel, 1981), and in the unscheduled DNA synthesis of cultured HeLa cells (Martin and McDermid, 1981) in the absence but not presence of a microsomal metabolic activating system. Intraperitoneal injection of 100 mg ETU/kg to mice resulted in 96% inhibition of ^{3}H-thymidine incorporation into DNA (Seiler, 1977a). ETU also was positive in the mitochondrial DNA petite mutation assay in Saccharomyces cerevisiae (Diala et al., 1980; Egilsson et al., 1979). Several of the studies using S. typhimurium considered the negative response to ETU to be a false-negative response in view of the known carcinogenic potential of the compound (Baker and Bonin, 1981; Venitt and Crofton-Sleigh, 1981; Rowland and Severn, 1981; Brooks and Dean, 1981).

In addition to the studies summarized in Table 5-6, Seiler (1975, 1977b) reported positive results using ETU in combination with $NaNO_2$ (N-nitroso-ETU) in the S. typhimurium reverse mutation assay and in micronuclei formation in bone marrow erythrocytes from N-nitroso-ETU-treated mice. The N-nitroso-ETU gave greater responses than either $NaNO_2$ or ETU alone.

TABLE 5-6

Genotoxicity Testing of ETU

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response[a]	Comment	Reference
Reverse mutation	S. typhimurium strain G46	spot test	10-25,000 ppm	- S9	+	weakly positive with dose response at ≥10 ppm. It was unclear as to what the ppm referred (i.e., the concentration on the plate or in the drop applied to the plate).	Seiler, 1974
Reverse mutation	S. typhimurium						
	G46	plate incorporation	0, 20, 40, 80 or 200 mg/plate	NR	-	+ ≥20 mg/plate with dose response increase; positive results were also observed in a spot test.	Schupbach and Hummler, 1976; 1977
	TA1530	plate incorporation			+		
	TA1531	plate incorporation			-		
	TA1532	plate incorporation			-		
	TA1964	plate incorporation			-		
Reverse mutation	S. typhimurium						
	TA1535	plate incorporation	0, 10, 100, 1000 or 10,000 µg/plate	± S9	±	+ only at concentration of 10,000 µg/plate without metabolic activation	Teramoto et al., 1977; Shirasu et al., 1976a
	TA1536	plate incorporation		± S9	-		
	TA1537	plate incorporation		± S9	-		
	TA1538	plate incorporation		± S9	-		
	G46	plate incorporation		± S9	-		
Reverse mutation	S. typhimurium						
	TA1535	plate incorporation	0, 5000, 10,000, 15,000 or 20,000 µg/plate	± S9	±	+ at ≥5000 µg/plate with dose response increase without S9.	Teramoto et al., 1977
	TA100	plate incorporation		± S9	-		
Reverse mutation	S. typhimurium					NC	
	TA1535	plate incorporation	0-1000 µg/plate	± S9	-		Baker and Bonin, 1981
	TA1537	plate incorporation	0-1000 µg/plate	± S9	-		
	TA1538	plate incorporation	0-1000 µg/plate	± S9	-		
	TA98	plate incorporation	0-1000 µg/plate	± S9	-		
	TA100	plate incorporation	0-1000 µg/plate	± S9	-		
Reverse mutation	S. typhimurium					NC	
	TA98	plate incorporation	0.5-100 µg/plate	± S9	-		Venitt and Crofton-Sleigh, 1981
	TA100	plate incorporation	or 10-500 µg/plate	± S9	-		
Reverse mutation	S. typhimurium					NC	
	TA1535	plate incorporation	0.1-2000 µg/plate	± S9	-		Rowland and Severn, 1981
	TA1537	plate incorporation		± S9	-		
	TA1538	plate incorporation		± S9	-		
	TA98	plate incorporation		± S9	-		
	TA100	plate incorporation		± S9	-		

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response[a]	Comment	Reference
Reverse mutation	S. typhimurium TA1537	plate incorporation	NR	± S9	-	NC	Nagao and Takahashi, 1981
	TA98	plate incorporation		± S9	-		
	TA100	plate incorporation		± S9	-		
Reverse mutation	S. typhimurium TA1535	plate incorporation	0.2-2000 µg/plate	± S9	-	NC	Brooks and Dean, 1981
	TA1537	plate incorporation		± S9	-		
	TA1538	plate incorporation		± S9	-		
	TA98	plate incorporation		± S9	-		
	TA100	plate incorporation		± S9	-		
	TA92	plate incorporation		± S9	-		
Reverse mutation	S. typhimurium G46	host-mediated rats, bacteria injected i.p.	3 x 200 mg/kg	NA	-	NC	Teramoto et al., 1977
			3 x 400 mg/kg orally	NA	-		
	G46	host-mediated mice, bacteria injected i.p.	3 x 200 mg/kg	NA	-		
			3 x 400 mg/kg orally	NA	-		
Reverse mutation	S. typhimurium TA1530	host-mediated mice, bacteria injected i.p.	0-6000 mg/kg intramuscularly	NA	+	weakly (2.4 times) but significantly increased at 6000 mg/kg	Schupbach and Hummler, 1976, 1977
	G46	host-mediated mice, bacteria injected i.p.	0-6000 mg/kg intramuscularly	NA	-		
Reverse mutation	E. coli WP2 hcr+	NR	0-10,000 µg/plate	± S9	-	NC	Teramoto et al., 1977; Shirasu et al., 1976a
	hcr-	NR	0-10,000 µg/plate	± S9	-		
Reverse mutation	E. coli WP2 Blr	plate incorporation	NR	± S9	-	NC	Matsushima et al., 1981
	WP2 uvrA	plate incorporation	NR	± S9	-		
	WP2 uvrA/ pkM 101	plate incorporation	NR	± S9	-		
Reverse mutation	E. coli WP2 (p)(pkM101)	plate incorporation	0.5-100 µg/plate or 10-500 µg/plate	± S9	-	NC	Venitt and Crofton-Sleigh, 1981
	WP2 uvr (p) (pkM101)	plate incorporation	0.5-100 µg/plate or 10-500 µg/plate	± S9	-		

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response[a]	Comment	Reference
Rec assay	B. subtilis H17 Rec$^+$	spot test (inhibition of growth)	20-4000 µg/disk	NR	-	no growth inhibition zone at any concentration	Teramoto et al., 1977; Shirasu et al., 1976a
	M45 Rec$^-$		20-4000 µg/disk	NR	-		
Rec assay	B. subtilis spores	spot test (inhibition of growth)	2 mg/disk max. dose	± S9	+	without metabolic activation, ETU was weakly +	Kada, 1981
				+ S9 (rat)	-	with S9 from fish, there was a killing effect without DNA damage	
				± S9 (yellowtail fish)	-		
Mitotic cross-over	S. cerevisiae T_1	plate incorporation	1000 µg/mL	± S9	-	NC	Kassinova et al., 1981
	T_2	plate incorporation	1000 µg/mL	± S9	-		
Repair test	S. cerevisiae T_4	spot test	50 µL of a 0.1-1.0% solution	- S9	-	NC	Kassinova et al., 1981
	T_5	spot test	50 µL of a 0.1-1.0% solution	- S9	-		
Petite mutation mitochondrial DNA	S. cerevisiae	plate incorporation	0.5-2.0 mg/mL	NR	+	slight but positive response	Diala et al., 1980
Petite mutation mitochondrial DNA	S. cerevisiae	plate incorporation	5.00 mM	NR	+	NC	Egilsson et al., 1979
Sex-linked recessive lethal	D. melanogaster xy/o males mated with Berlin females	NR	2.5% ETU in sugar water	NR	-	NC	Mollet, 1975
Rate of dominant lethals	D. melanogaster gametes from xy/o males x Berlin females	NR	4 concentrations (not specified)	NR	-	The rate of dominant lethals increased slightly with high concentrations, but not significantly.	Mollet, 1975
Chromosome aberrations	Chinese hamster DON cells	cell culture	1000 µg/mL 3200 µg/mL	NR	-	severe cytotoxic effect at 3200 µg/mL	Teramoto et al., 1977; Shirasu et al., 1976b

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response[a]	Comment	Reference
Cell transformation	Baby hamster kidney cells	cell culture	LC_{50} >8000 µg/mL	± S9	+ +	NC	Daniel and Dehnel, 1981
Unscheduled DNA synthesis	rat hepatocytes hepatocytes	cell culture	3.2×10^{-9}M to 9.6×10^{-9}M/plate	none	-	NC	Althaus et al., 1982
Unscheduled DNA synthesis	HeLa cells	cell culture	0.1-100 µg/mL	± S9	±	+ without metabolic activation	Martin and McDermid, 1981
Chromosome aberrations	rats	orally	200 or 400 mg/kg or 2-5 x 50-400 mg/kg at 24-hr intervals	NA	- -	There was increased frequency of numerically aberrant bone marrow cells of treated animals, but it was not statistically significant.	Teramoto et al., 1977; Shirasu et al., 1976b
Dominant lethal	mice	male mice treated orally then mated	300 or 600 mg/kg for 5 days	NA	-	no differences in numbers of corpus lutea, implantations and live embryos compared with controls	Teramoto et al., 1977; Shirasu et al., 1976c
Dominant lethal	mice	male mice treated orally then mated	500, 1000 or 3500 mg/kg	NA	-	NC	Schupbach and Hummler, 1976, 1977
Micronucleus test	mice	2 oral doses, 24 hours apart	700, 1850 or 6000 mg/kg	NA	-	NC	Schupbach and Hummler, 1976, 1977
Inhibition of DNA synthesis	mice	i.p. injection	100 mg/kg	NA	+	96% inhalation of ^{3}HTdR incorporation	Seiler, 1977a

NA = Not applicable; NC = No comment; NR = Not reported

[a]Responses: +, positive; -, negative; =, negative with and without S9 activation system; ±, positive with and negative without S9 activation system; ∓, negative with and positive without S9 activation system

5.3. TERATOGENICITY

Table 5-7 summarizes studies of ETU teratogenicity in a number of species and under a variety of exposure and observation conditions. ETU was a potent teratogen in rats at daily oral doses as low as 20-40 mg/kg during gestation with no toxicity to dams (Khera, 1973; Khera and Tryphonas, 1977; Chernoff et al, 1979; Teramoto et al., 1975a). The fetal responses include CNS abnormalities such as exencephaly, hydrocephalus, hydranencephalus, meningoencephalus and meningorrhea (Khera, 1973; Ruddick and Khera, 1975; Khera and Tryphonas, 1977; Chernoff et al., 1979; Lu et al., 1980; Mungkornkarn and Bal, 1978). Skeletal anomalies were also observed by these investigators. ETU did not appear to be teratogenic to rabbits (Khera, 1973), cats (effects were seen at doses that were maternally toxic) (Khera and Iverson, 1978), mice or guinea pigs (Chernoff et al., 1979). Teramoto et al. (1980b) did observe some teratogenic effects in mice, however, that were fed ETU in combination with sodium nitrite (study not included in Table 5-7). CNS and skeletal defects were produced in offspring of hamsters treated with ETU at relatively high single oral dose levels of $\geq$1200 mg/kg (Khera et al., 1980), although Lu et al. (1980) found fetal abnormalities in hamsters at repeated doses of $\geq$120 mg/kg and CNS defects with multiple doses of 300 or 360 mg/kg (Lu et al., 1980; Su et al., 1981).

Dermal application of ETU to pregnant rats at a relatively low dose of 50 mg/kg/day for 2 gestational days also resulted in CNS and skeletal abnormalities in fetuses (Stula and Krauss, 1977); however, inhalation of ETU aerosols (Dilley et al., 1977) or intraamniotic injections of ETU (Teramoto et al., 1980a) produced no teratogenic effects in rats.

Details of experimental protocols and progression of abnormalities during organogenesis and postnatally are given in Table 5-7.

TABLE 5-7

Studies on the Potential Teratogenicity of ETU

Route	Species, Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Oral	rat/Wistar	10 controls 53 treated	distilled water	0, 5, 10, 20 or 40 mg/kg	21-42 day of pre-pregnancy to day 15 of gestation	22[a]	none	CNS deformities: exencephaly meningoencephalocele, meningorrhea, hydrocephalus, agenetic cerebellum, disoriented ependymal layer, obliterated neural canal. Skeletal defects: abnormal pelvic limb, caudal abnormalities. These effects were seen in all experimental rats in a dose-related manner. -No effects were observed below 10 mg/kg ETU.	Khera, 1973
Oral	rat/Wistar	13 controls 52 treated	distilled water	0, 5, 10, 20, 40 or 80 mg/kg	6-15	22	80 mg/kg for 7 days produced 9/11 deaths		
Oral	rat/Wistar	17 controls 64 treated	distilled water	0, 5, 10, 20 or 40 mg/kg	7-20	22	none		
Oral	rabbit/ New Zealand	7 controls 26 treated	distilled water	0, 10, 20, 40 or 80 mg/kg	7-20	30[b]	none	Increased number of resorption sites and decreased brain weight at 80 mg/kg.	Khera, 1973
Oral	rat/Wistar	NR - a total of 80 litters from treated dams were examined	distilled water	240 mg/kg	one of days 6-21	22[a]	none	When exposed on day 6, 7, 8 or 9 no malfunctions were seen. -day 10 - defective external genitalia (6%), hydronephrosis (20%), absent or short tail (20%). -day 11 - spina bifida (30%), fused ribs (100%), renal abnormalities (75%), caudal anomalies (100%). -day 12-15 - hydrocephalus (91%), exencephaly (91%), brachygnathia (68%), forelimb micromelia (90%), scoliosis (100%), renal abnormalities (100%). -day 16 - hydranencephaly (100%), cleft palate (100%), kidney anomalies (100%). -day 17-19 - hydranencephaly and renal defects (100%). -day 20 or 21 -renal defects only (20 and 42%).	Ruddick and Khera, 1975

TABLE 5-7 (cont.)

Route	Species, Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Oral	rat/Wistar	6-12/group	distilled water	0, 30 or 45 mg/kg	15[a]	first day of birth up to 9 weeks of age	NR	High postnatal mortality: all at 45 mg/kg died by 9 weeks; at 30 mg/kg 90/155 compared with 9/187 controls. Hydrocephalus and microphthalmia: at 45 mg/kg, 25/49; at 30 mg/kg, 63/70 of the pups, and all 63 died within 9 weeks at birth. Motor defects were seen in surviving pups. F_1 females were allowed to mate and proved to be fertile and bear normal progency. Cross fostering experiments showed that the observed defects were produced in utero.	Khera and Tryphonas, 1977
Oral	rat/Wistar	5-10/group	distilled water	0, 15 or 30 mg/kg	15[a]	day of birth up to 64 weeks of age.	NR	No adverse effects were observed at 15 mg/kg. At 30 mg/kg, moderate hydrocephalus, 8 pups had abnormal gait.	Khera and Tryphonas, 1977
Oral	rat/Wistar	13	distilled water	0 or 45 mg/kg	15[a]	17, 20 and 22 of gestation or 2.7, 10 or 15 postnatal.	NR	Hydrocephalus not grossly observed in 17, 20 or 22-day fetuses or in 1 or 2-day-old pups. -stillborn pups: 6/8 were hydrocephalic -7-day-old pups: 11/13 mild hydrocephalus compared with 0/13 controls -10-day-old pups: 11/12 moderate hydrocephalus (0/13 control) -15-day-old pups: 9/10 with severe hydrocephalus (0/15 control) Histology: 17-day fetuses- cellular necrosis in brain, moderate spongy changes, subependymal plate throughout neuraxis, reduced brain mass. 20-day fetuses- rosette formation indicating regeneration 2-day-old pups - necrosis and spongy changes	Khera and Tryphonas, 1977

TABLE 5-7 (cont.)

Route	Species, Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
								7-day-old pups - patchy disorganization and thinning of cerbral cortex-progressive neural and ependymal necrosis to 15 days.	
Oral	cat	14 controls 41 treated	gelatin capsule	0, 5, 10 30, 60 or 120 mg/kg	16-35	46[a]	progressive weight loss, ataxia, tremors, hind limb paralysis in 24 cats at ≥10 mg/kg. 11 cats died or were killed in moribund state. At term, there were 10 treated cats and 7 control cats.	No treatment-related effect on mortality or fetal weight. Incidence of anomalies were 1/12 for 120 mg/kg group, 0/10 for 30 mg/kg, 1/4 for 5 mg/kg and 0/33 for controls. One fetus had exencephaly, hydrocephaly and cleft palate; another had kyphoscoliosis and umbilical hernia. 11/35 live fetuses from cats killed in moribund conditions were malformed with coloboma in 4, umbilical hernia in 4, cleft palate in 2 and spina bifida in 1.	Khera and Iverson, 1978
Oral	hamster/ Syrian Golden	NR	aqueous gelatin suspension	600, 1200, 1800 or 2400 mg/kg	11[c]	term	none	-increased mortality and reduced weight at 2400 mg/kg -dose related anomalies at ≥1200 mg/kg hydrocephalus - 11-61% (range for dose 1200-2400 mg/kg) hypoplastic cerebellum - 4-72%; cleft palate - 17-85%; delayed calvarial ossification - 0-51%; ectrodactyly - 0-13%	Khera et al., 1980
Oral	mouse/CD-1	66	distilled water	0, 100 or 200 mg/kg	7-16	18[a]	at 200 mg/kg, increased liver/body weight	at 200 mg/kg - increased number of ribs ($p<0.05$)	Chernoff et al., 1979

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TABLE 5-7 (cont.)

Route	Species, Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Oral	rat/ Sprague-Dawley	109	distilled water	0, 5, 10, 20, 30, 40 or 80 mg/kg	7-21	21[a]	25% mortality at 80 mg/kg	increased mortality, decreased body weight, decreased ossification, skeletal defects, CNS defects (hydrocephalus, encephalocele) cleft palate in majority of fetuses at 80 mg/kg ($p<0.001$). At 40 mg/kg-reduced fetal weight and ossification, high rate of CNS defects (not as much as at 80 mg/kg). Hydrocephalus was seen in some fetuses at 20 and 30 mg/kg. No effect at 10 mg/kg.	Chernoff et al., 1979
Oral	hamster/ Ela: ENG	49	distilled water	0, 25, 50 or 100 mg/kg	5-10	15[a]	none	No treatment-related abnormalities	Chernoff et al., 1979
Oral	guinea pig/ Hartley	NR	distilled water	0, 50 or 100 mg/kg	12	20[b]	none	No treatment-related abnormalities	Chernoff et al., 1979
Oral	hamster/ Golden	NR	distilled water	0, 60, 120, 300 or 600 mg/kg (I)	7-14	NR	none	at $\geq$120 mg/kg- short snout, missing innominate artery, edema, reduced number of lung lobes, bent digits, hydroureter, fused ribs and fused sternebrae at 60 mg/kg - cleft palate	Lu et al., 1980
Oral	hamster/ Golden	NR	distilled water	0, 300 or 360 mg/kg 3x/day (II)	7-11	NR	none	Resorption rate higher than in III. Cleft palate, oligodactyly, meningorrhea, micrognathia, hydroureter, hydronephrosis, fused digits, fused ribs, missing ribs and renal agenesis in II and III.	Lu et al., 1980
Oral	hamster/ Golden	NR	distilled water	0 or 360 mg/kg 3x/day (III)	10-11	NR	none	Meningocele, exencephaly, anophthalmia, edema, short trunk, undescended testes, decreased number of lung lobes in II, hyperplastic limbs in III.	Lu et al., 1980

TABLE 5-7 (cont.)

Route	Species, Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Oral	rat/Wistar	NR	NR	50-200 mg/kg	one of days 6-14	20[b]	NR	No effect on viability, no anomalies on day 6-8; on day 9 or later, meningocele, microagnathia, cleft palate and atresia, short tail, hyperplastic digits. These effects were dose related.	Teramoto et al., 1975a
Oral	rat/Wistar	NR	NR	100 mg/kg	12	13[b] 14 or later	NR	Extensive cell necrosis in neutral tube at day 13; at day 14 or later, rosette formation indicated regeneration but development was inhibited.	Teramoto et al., 1975b
Oral	rat/Wistar	5 controls 20 treated	distilled water	0 or 300 mg/kg	12	22[c]	NR	Reduced body weight. Of 196 fetuses from treated dams 38% had exencephaly, 30% hydrocephalus (also short or absent tail), 20% hydroencephaly associated with agnathia, micrognathia, abnormal limbs and tails.	Mungkornkarn and Bal, 1978
Oral	hamster/ Golden	NR	distilled water	0 or 360 mg/kg 3x day	8, 9, 10 or 11	15[a]	none	fetal weight was significantly reduced in 8 or 9 day groups. Increased incidence in resorption in 8 or 9 day fetuses, not in 11. Common malformations were cleft palate, menigocele, meningorrhea, and oligodactyly. On day 8 - enlarged kidney, exencephaly edema, micromelia, microstoma. On day 9 - amelia, anal atresia, cleft lip, renal agenesis and short neck. On day 10 - bent digit, fused digits, renal agenesis and wavy rib. On day 11 - hydronephosis, hydroureter, hyperplastic limb, open eye, undescended testes.	Su et al., 1981

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TABLE 5-7 (cont.)

Route	Species, Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day	Maternal Response	Fetal Response	Reference
Dermal	rat/Charles River CD	8	DMSO	50 mg/kg/day	10 and 11	20[a]	none	3/83 - short tail, 2/83 - fused ribs, 1/40 vehicle control had encephalocele	Stula and Krauss, 1977
Dermal	rat/Charles River CD	5	DMSO	25 mg/kg/day	10 and 11	20[a]	none	No abnormalities	Stula and Krauss, 1977
Dermal	rat/Charles River CD	6	DMSO	50 mg/kg/day	12 and 13	20[a]	none	No effect on mortality; reduced fetal weight. 73/73 malformed fetuses with encephalocele, missing tail, missing leg bones, hunchback, short mandible, fused ribs, fused sternebrae. No abnormal controls.	Stula and Krauss, 1977
Inhalation	rats/ Strain NR	NR	aerosol	120.4 mg/m³	7-14	20[c]	NR	Increased fetal mortality, decreased fetal weight, no terata effects	Dilley et al., 1977
Intraamniotic injection	rat/Wistar	NR	NR	200 mg/kg	12	20[b]	none	No effect on survival, weight or development.	Teramoto et al., 1980a

[a]First day of gestation designated day one.

[b]First day of gestation designated day zero.

[c]First day of gestation not designated.

NR = Not reported

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A target organ of ETU carcinogenicity (see Section 5.1.) and toxicity (see Section 5.3.) is the thyroid gland. Lu and Staples (1978) conducted a teratogenicity study in rats in which the dams had altered thyroid function (either by thyroidectomy or by administration of thyroxine). ETU was given to hypothyroid, euthyroid or hyperthyroid pregnant rats at a dose of 40 mg/kg from days 7-15 of gestation, and, although fetuses were found to be abnormal on day 20, the abnormalities were not related to maternal thyroid status.

5.4. OTHER REPRODUCTIVE EFFECTS

No morphological anomalies were observed in pups born to rats that received 30 mg ETU/kg/day orally from day 7 of pregnancy to day 15 post-partum, although 4 of 9 litters died within 24 hours of delivery. Two more litters died during the first postnatal week; the pup of the surviving litters developed hydrocephaly. The dams were observed to have milk, but they failed to nurse (Kavlock and Chernoff, 1978).

Lactating rats given ETU at single oral doses of 20, 50, 75 or 100 mg/kg continued to nurse their pups. The pups had increased thyroid weights at all dose levels and decreased survival rates at the two highest exposure levels, and developed hypoproteinemia with increased serum aminopeptidase activity at 100 mg ETU/kg (Lewerenz and Schnaak, 1978).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Graham and Hansen (1972) studied the effects of feeding ETU to groups of 20 male Osborne-Mendel rats, at dietary levels of 0, 50, 100, 500 and 750 ppm for up to 120 days, on the thyroid gland morphology and uptake of ^{131}I. At 30-day intervals, rats were killed at 4 or 24 hours following an i.p. injection of 5 µCi ^{131}I. Four hours after injection, the uptake of ^{131}I (cpm/mg tissue) was statistically significantly decreased at the 500

and 750 ppm levels at each interim kill. At 24 hours after injection, the decreased ^{131}I uptake was statistically significant at 100 ppm ETU. Histological examination revealed no difference in the thyroid of rats fed 50 ppm ETU for 90 days, but slight hypertrophy was evident at the 100 ppm level, becoming progressively more marked at 500 and 750 ppm ETU, with evidence of adenoma at these levels.

The feeding of ETU at levels of 0, 1, 5, 25, 125 or 625 ppm in the diet for up to 90 days produced toxic effects in rats at ≥125 ppm ETU as evidenced by altered thyroid function and morphology (Freudenthal et al., 1977). Serum levels of triiodothyronine and thyroxine, and iodine uptake were reduced in rats fed 625 ppm ETU. Serum TSH levels were elevated in both the 125 and 625 ppm groups. Because no consistent effects were observed at 25 ppm, the authors considered this level of ETU in the diet to be a no-effect level for subchronic exposure.

Charles River rats were fed ETU in the diet at levels of 0, 5, 25, 125, 250 or 500 ppm for 2, 6 or 12 months (Graham et al., 1973). Each group consisted of 68 males and 68 females. Ten animals of each sex were given i.p. injections of 5 μCi ^{131}I at the end of each feeding period and killed after a 24-hour fast for analysis of ^{131}I uptake (cpm/mg thyroid tissue) and for organ-to-body weight ratio measurement. Additional rats not injected with ^{131}I were also killed for histological examination of tissues after 6 and 12 months. In animals fed ETU for 2 months, liver-to-body weight ratios were significantly higher at ≥125 ppm ETU than were control ratios. At the 500 ppm level, male rats had increased ratios for kidneys and testes. The thyroid gland was the most affected tissue with significantly increased thyroid-to-body weight ratios at ≥250 ppm ETU for males and ≥125 ppm levels for females ($p<0.001$) when compared with control

rats. The uptake of ^{131}I was decreased for males at 500 ppm ETU for 12 months. For females, ingestion of ≥125 ppm ETU for 6 months caused decreased ^{131}I uptake, while for 12 months at these levels, uptake increased. The pattern of increased organ-to-body weight ratios at 6 and 12 months was similar to that at 2 months, with the thyroid weight increasing up to 18 times the control value. Comprehensive histological examination of tissues from 5 male and 5 female rats fed at the 500 ppm level for 6 months revealed hyperplastic thyroids with adenomatous nodules and some carcinomas, but no treatment-related changes in other organs.

Examinations of tissues from 9-13 rats/group treated for 12 months revealed morphological changes in the thyroid at all dose levels, progressing from nodular hyperplasia in the 125 ppm males to carcinomas in 23% of the 250 ppm and 77% of the 500 ppm males, and from acinar epithelium papillation and parafollicular capillaries in the 5 ppm females to carcinomas in 42% of the 500 ppm females. The remaining animals in this study were continued on the feeding regimen for another year (Graham et al., 1975) with further thyroid tumorigenesis evident (see Section 5.1.).

Kameda (1982) fed three dogs a "diet containing a 0.1% ETU solution" for 6 months and observed thyroid glands hypertrophied to 30 times the size observed in normal control dogs, with histological changes in C cells (calcitonin secreting cells) and follicular cells. It was not clear whether the diet contained 0.1% ETU or if an undisclosed volume of a 0.1% solution was added to the diet.

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} for ETU was 3000 mg/kg for mice (Teramoto et al., 1980b) and 1832 mg/kg for rats (Graham and Hansen, 1972). The dose that was lethel to 50% of mice in 7 days ($LD_{50/7}$) after i.p. injection of ETU was 1770 mg/kg (Salamone, 1981).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The toxicity of ETU was examined in the creek chub, Semotilus atromaculatus (Gillete et al., 1952). A critical toxic range of 6000-8000 mg/ℓ was determined. The lowest value (6000 mg/ℓ) represents the concentration at which no test animals (n = 4/group) died during a 24-hour exposure (24-hour LC_0). The upper limit (8000 mg/ℓ) represents the level at which all creek chubs died within the 24-hour exposure (24-hour LC_{100}). The authors noted that volatilization of the test compound was possible, so actual toxic levels may be lower than the nominal concentrations (Gillete et al., 1952).

6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic ETU exposure in aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the toxic effects of ETU on algae or aquatic plants were not located in the available literature.

6.4. RESIDUE

Pertinent data regarding ETU residues in aquatic organisms were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Additional information relevant to the aquatic toxicity of ETU was not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

A NIOSH Current Intelligence Bulletin recommended that ETU be regarded in the workplace as a carcinogen and as a CNS teratogen (Stein et al., 1978). Based upon toxicity and carcinogenicity studies in animals, Kay (1974) also recommended that workers take care in handling pesticides containing ETU.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of ETU were not located in the available literature.

8. RISK ASSESSMENT

There is adequate evidence that ETU is a teratogen in rats and a carcinogen in mice and rats. The teratogenicity of ETU was evidenced by severe CNS abnormalities in rat pups at oral maternal doses as low as 20 mg ETU/kg, with no toxicity to dams (Khera, 1973; Khera and Tryphonas, 1977; Chernoff et al., 1979; Teramoto et al., 1975a).

The carcinogenicity of ETU was demonstrated in chronic feeding studies. In mice hepatomas were induced in both sexes of two strains, and there was increased incidence of lymphomas in females of one strain following 18 months of maintenance on diets containing 646 ppm of ETU (BRL, 1968; Innes, et al., 1969). In rats, the thyroid was the target organ for ETU carcinogenicity, with thyroid carcinomas induced in 6/52 Charles River rats fed 175 ppm and in 25/52 rats fed 350 ppm ETU for 18 months and observed for 6 months compared with 0/64 in controls (Ulland et al., 1972). Similar tumor incidences were reported by Weisburger et al. (1981) in this strain of rats at the same dietary levels. High incidences of thyroid adenocarcinomas (16/69 rats at 250 ppm; 62/70 rats at 500 ppm; 2/72 controls) were induced in Charles River rats by dietary administration of ETU for 2 years (Graham et al., 1975).

The Cancer Assessment Group of the U.S. EPA concluded that ETU was oncogenic in mice and rats (U.S. EPA, 1977) and NIOSH has recommended that ETU be handled as a carcinogen and as a teratogen in the workplace (Stein et al., 1978). IARC (1982) has concluded that evidence of ETU as a carcinogen to animals is sufficient, but the evidence of ETU as a carcinogen in humans is not adequate. In evaluating the carcinogenic risk of ETU to humans, IARC (1982) has assigned ETU to Group 2B ("probably carcinogenic to humans").

A carcinogenic potency factor (q_1^*) can be derived; however, it was difficult to decide which study, Ulland et al. (1972) or Graham et al. (1975), would give the most conservative estimate because of the differences in dose levels and numbers of animals studied. Using the data of Ulland et al. (1972) that the incidence of thyroid adenocarcinomas in male rats fed ETU in the diet for 18 months and observed for 6 additional months was 0/32, 3/26 and 17/26 for the control, the 175 ppm group and the 350 ppm group, respectively, a q_1^* of 1.83×10^{-1} $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 5.46×10^{-3} mg/kg/day or 3.82×10^{-2} mg/day for a 70 kg man.

Using the data of Graham et al. (1975) that the incidence of thyroid adenocarcinomas in male and female rats fed ETU in the diet for 2 years was 2/72 for controls, 2/75 at 5 ppm, 1/73 at 25 ppm, 2/73 at 125 ppm, 16/69 at 250 ppm and 62/70 at 500 ppm, a q_1^* of 3.627×10^{-2} $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 2.76×10^{-4} mg/kg/day, or 1.93×10^{-2} mg/day for a 70 kg man. Thus, the data of Graham et al. (1975) give a slightly more conservative risk level than do the data of Ulland et al. (1972), but the values are similar.

The q_1^* values were calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980). Complete data for the derivation of the q_1^* are presented in Appendices B and C.

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APPENDIX A

Literature Searched

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: Ethylene thiourea

Reference: Ulland et al., 1972

Species, Strain, Sex: Rat, Charles River, male

Body Weight: 0.35 kg (assumed)

Length of Exposure (l_e) = 548 days

Length of Experiment (L_e) = 730 days

Lifespan of Animal (L) = 730 days

Tumor Site and Type: thyroid gland, adenocarcinoma

Route, Vehicle: oral, diet

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0	0/32
175 ppm = 8.75 mg/kg/day	6.57	3/26
350 ppm = 17.5 mg/kg/day	13.1	17/26

Human $q_1^* = 1.83 \times 10^{-1}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 5.46×10^{-5} mg/kg/day = 3.82×10^{-2} mg/day for 70 kg man

APPENDIX C

Cancer Data Sheet for Derivation of q_1^*

Compound: Ethylene thiourea

Reference: Graham et al., 1975

Species, Strain, Sex: Rat, Charles River

Body Weight: 0.6 kg (measured)

Length of Exposure (l_e) = 730 days

Length of Experiment (L_e) = 730 days

Lifespan of Animal (L) = 730 days

Tumor Site and Type: thyroid gland, adenocarcinoma

Route, Vehicle: oral, diet

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0	2/72
5 ppm	0.25	2/75
25 ppm	1.25	1/73
125 ppm	6.25	2/73
250 ppm	12.50	16/69
500 ppm	25.0	62/70

Human $q_1^* = 3.63 \times 10^{-2}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 2.75×10^{-4} mg/kg/day = 1.93×10^{-2} mg/day for 70 kg man